

EDITORIAL COMMENT

Frailty Among Asian Patients With Heart Failure*



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Although the concept of frailty is easy to recognize and frequently used, a gold standard definition or method of assessing frailty has been elusive to date. The concept of frailty is often described as a state of diminished physiological reserve such as muscle, weight, and strength loss, with increased susceptibility to adverse outcomes, including falls, hospitalization, institutional placement, disability, and mortality (1). Frailty, although associated with advanced age, likely represents a distinct process in relation to chronic disease states.

The role of frailty has garnered attention in relation to cardiovascular disease. Heart failure (HF) in particular shares similar features with frailty, including advanced age, high comorbidity burden, exercise intolerance, reduced skeletal muscle, and cachexia (2). Consequently, it is becoming increasingly important to understand frailty in the context of HF treatment and outcomes. Frailty in HF seems to be common, with analysis of HF trials such as TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist), PARADIGM-HF (Prospective Comparison of ARNI with an ACE-Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure), and ATMOSPHERE (Aliskiren Trial to Minimize Outcomes in Patients with Heart Failure) Trial revealing that 94%

of HF patients with preserved ejection fraction and 63% of HF patients with reduced ejection fraction met criteria for frailty with an increased risk of adverse events, including mortality (3,4). Assessing frailty in HF is not without challenges, however. Many of the pre-existing, validated frailty assessment methods are time-consuming (making it difficult to use during routine clinical visits), require special equipment and instruments (eg, hand grip), and have been validated and used in limited specialty areas such as device and surgical settings, including transcatheter aortic valve replacement and heart transplantation (5).

In this issue of *JACC: Asia*, the paper by Aung et al (6) is significant in several aspects. First, the authors used a cumulative deficits approach to construct a frailty index (FI) using available baseline data points from the ASIAN-HF (Asian Sudden Cardiac Death in Heart Failure) registry. The investigators constructed a 48-item FI developed by Rockwood et al to assess health deficits and 15 questions from the Kansas City Cardiomyopathy Questionnaire to evaluate quality of life. Although the cumulative deficits approach is not without inherent culpability, using such an approach easily allows construction of an FI from a broader range of clinical trials and existing databases, both prospectively and retrospectively. Considering the features that HF and frailty share and how common frailty is in HF, little is known about frailty in HF. Only by expanding our knowledge of frailty in HF can we improve mitigation, reversal, and prevention of frailty in HF. Second, the ASIAN-HF registry is the first prospective multinational Asian registry of patients with symptomatic HF. To date, pre-existing information regarding frailty in HF has mainly been evaluated in patients of White race (78% for TOPCAT and 73% for PARADIGM-HF and ATMOSPHERE, both for the frailty analyses), with only a minority of patients of Asian race; there were 15% Asian patients for the PARADIGM-HF and ATMOSPHERE analysis, and the exact numbers were not reported for the TOPCAT

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trial but are expected to be small given that 89% of the study population was White.

Although Asian populations are often grouped together in clinical trials, it is important to note that these populations comprise diverse ethnicities with distinct cultures, genetics, and social experiences. There may be significant differences in age and body mass index as well as lean muscle mass compared with Western populations (7). Data evaluating frailty among Asian subjects with HF are scarce and further complicated by lack of validated frailty assessment tools within this population.

Results from the ASIAN-HF registry (6) revealed that among 3,881 participants, the mean FI was 0.28 ± 11 , with 69% of the population considered frail (FI >0.21). Frailer patients were older and more likely to be of Malay ethnicity and Southeast Asian residence. Frailty was associated with more comorbidities, most notably hypertension, coronary artery disease, chronic kidney disease, and diabetes ($P < 0.0001$), although there was no difference in body mass index across frailty groups. Compared with the non-frail group, FI classes 2 and 3 had increased risk of death or HF hospitalization within 1 year; these findings persisted after multivariable adjustment (class 2 adjusted hazard ratio: 1.49 [95% confidence interval: 1.13–1.97]; class 3 adjusted hazard ratio: 2.69 [95% confidence interval: 2.06–3.50]). The association between frailty class and composite outcomes was modified by ethnicity ($P_{\text{interaction}} = 0.0097$) and was strongest among Chinese patients but did not differ between sexes ($P_{\text{interaction}} = 0.186$) or HF type ($P_{\text{interaction}} = 0.094$).

This study (6) provided key insights related to frailty and HF within Asian populations. Despite the relative youth of this cohort, there was a high prevalence of frailty with a predisposition toward patients from Malaysia and Southeast Asia. Frail patients were less likely to be on guideline-directed medical therapy, had a higher risk of death or hospitalization from HF, and had a worse quality of life. Although use of guideline-directed medical therapy at target doses is known to reduce morbidity and mortality in HF with reduced ejection fraction, in clinical practice many patients are either on insufficient doses or not on therapy at all (8); perhaps elucidation of the disconnect between evidence and practice with special attention to ethnic- and cultural-specific differences may provide translatable best practices to frailty treatment given the similarities that exist. The results highlight the significance of frailty in health outcomes and regional as well as ethnic differences within Asia. Interestingly, the association

of frailty with poor outcomes was strongest in Chinese patients despite a higher prevalence of frailty in patients from Malaysia and Southeast Asia. Investigators postulated that this finding may have been due to socioeconomic determinants such as strong social support, which is likely a protective factor. Given the breadth of diversity within Asian populations, qualitative and quantitative studies evaluating the unique characteristics that exist among Asian ethnicities may be a worthwhile endeavor to determine if there are protective factors present that can be instituted on a larger scale.

Because frailty is a potentially reversible process, understanding its role in HF is important to consider for treatment and prevention (9). Other noteworthy strengths of this paper by Aung et al (6) include the study design, which allowed for comparisons of ethnicity and region within the cohort, and efforts to validate a well-known frailty assessment tool within the HF population. The latter point is of particular interest in relation to frailty screening and treatment monitoring in patients with HF. As discussed by Pandey et al (10), there are limitations associated with the deficits approach, including accurate recording of variables, inclusion of nonmodifiable deficits, and the need for a robust infrastructure to design and program this model into electronic medical records and health systems. Nonetheless, findings from ASIAN-HF are important for establishing a frailty assessment tool that over time can be adapted for easy administration in office settings and incorporated as a surveillance tool. Similar to methods used for monitoring response to HF treatment, this may also be the case for frailty in the future. Although the study comprised an ethnically and culturally diverse patient population, the results may be less generalizable to Asian subjects who have immigrated to other countries. Data regarding gait speed, an objective indicator often used as a surrogate for mobility in frailty assessments, were not available.

There is a promising suggestion that frailty in HF may at least partially be reversible or preventable through cardiac rehabilitation or prehabilitation, and a better understanding of frailty in Asian cohorts may provide unique potential mechanisms for intervention (11).

ASIAN-HF provides invaluable information to an emerging field in the literature with a population that has not been well studied previously. More prospective studies are needed to further characterize the relationship between frailty and HF, including additional elucidation of the mechanisms of disease,

protective factors, and the effect of treatment and prevention on HF outcomes.

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